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# Virtual clinical trials of BMP4-induced differentiation therapy identify strategies for combination with radiation therapy for glioblastoma patients

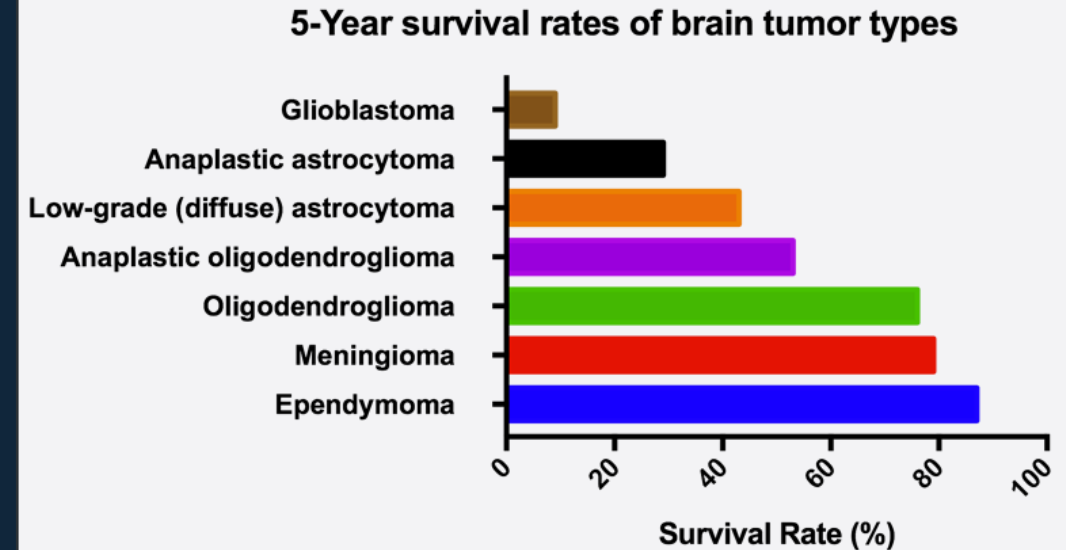
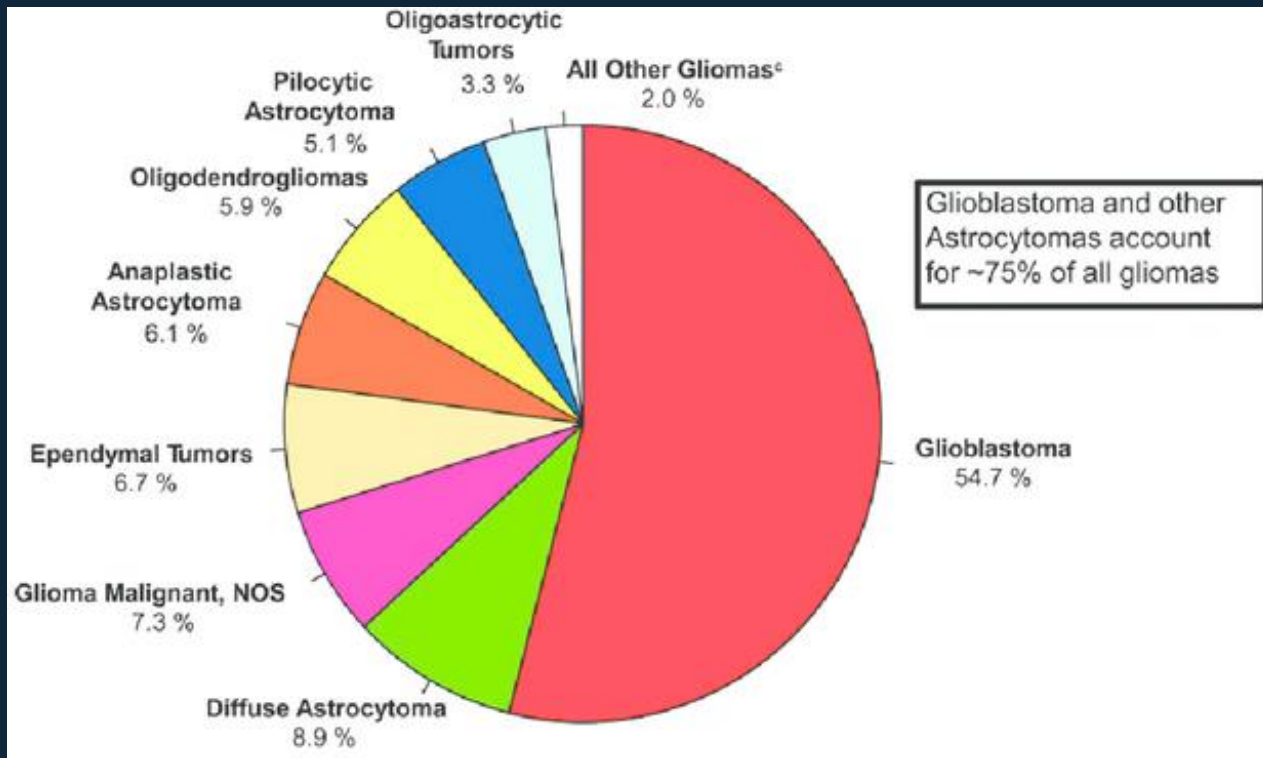
SMB MathEpiOnc

Nicholas Harbour, Markus Owen, Matthew Hubbard, Lee Curtin, Kristin Swanson

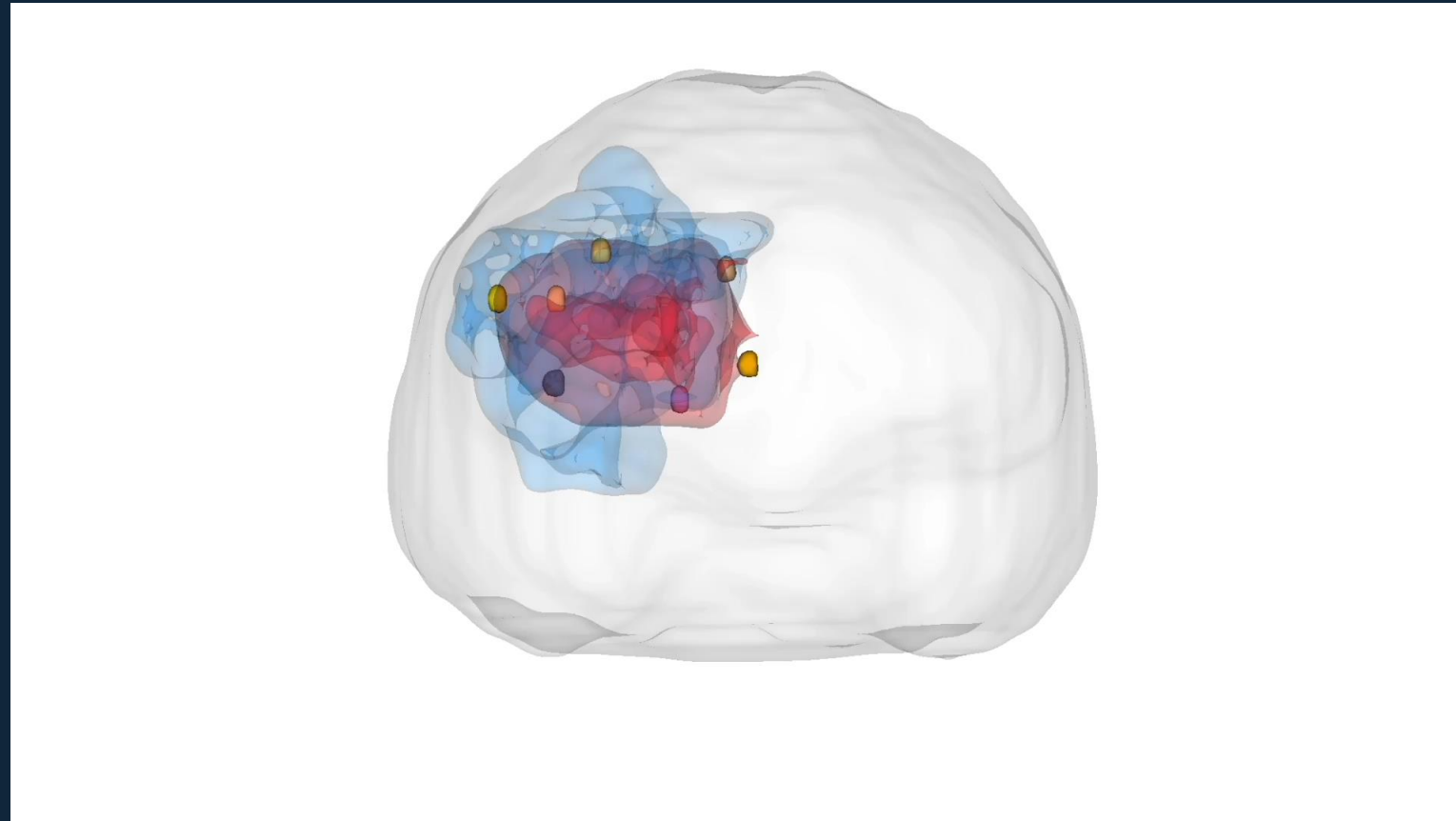
# Glioblastoma (GBM)

GBM is the most common primary malignant brain tumour (USA 2007-2011)

GBM has 5-year survival rate of only 5%

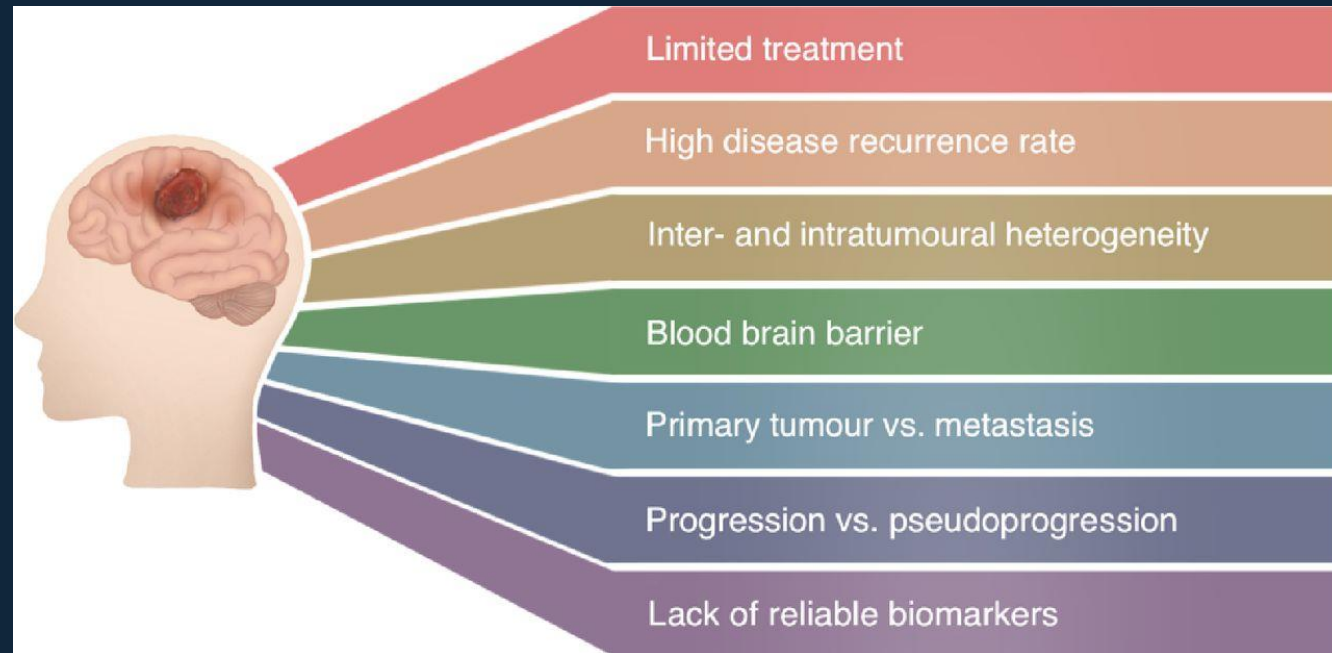
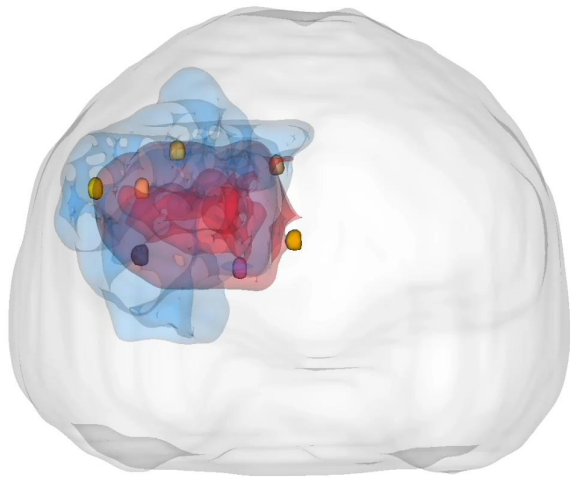


# Current standard of care in GBM

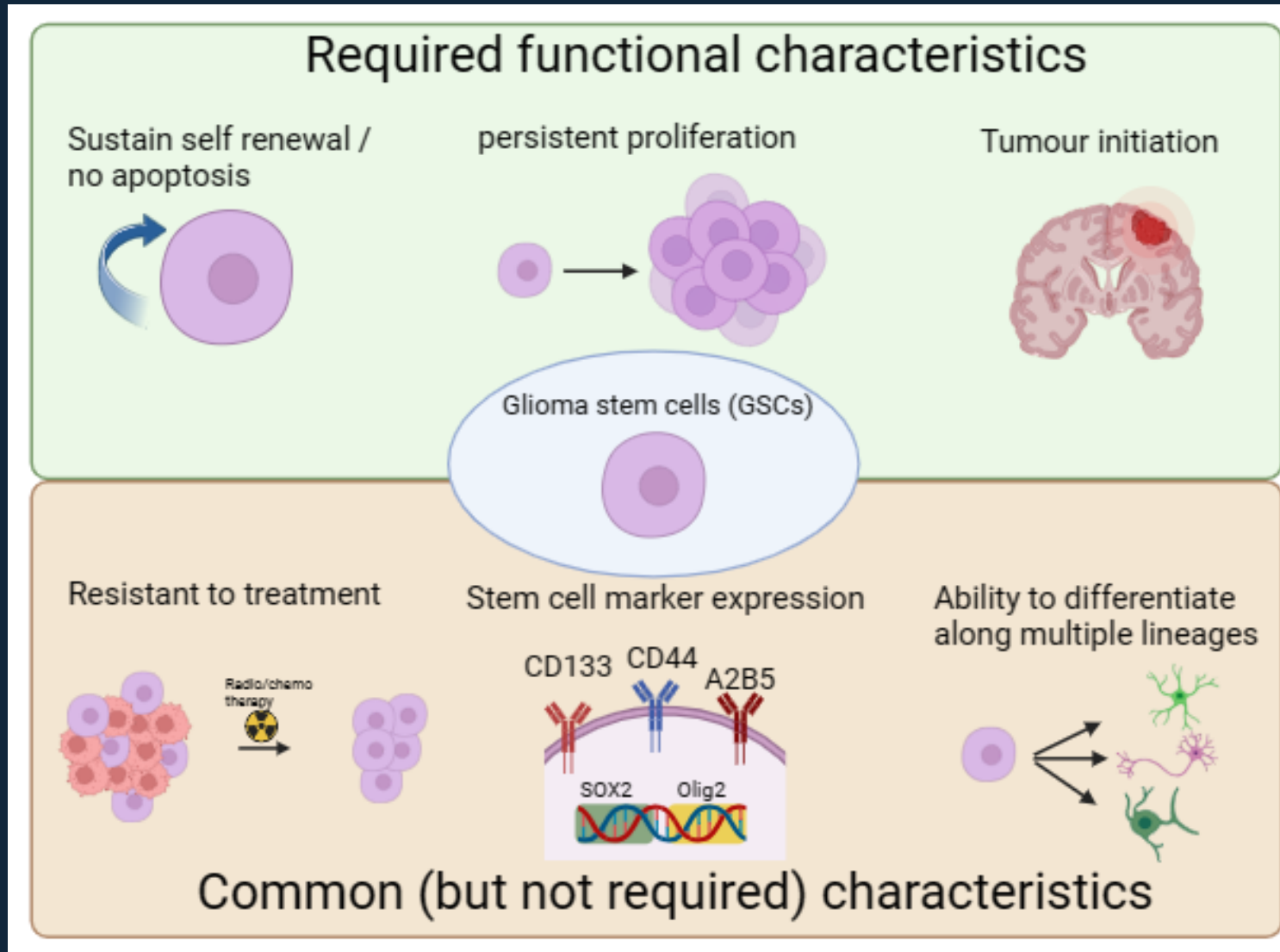


# Why does standard of care fail

- 1) GBM is highly diffuse – complete surgical resection is impossible
- 2) GBM is heterogenous – In particular a critical subpopulation, the glioma stem cells (GSCs) are highly resistant to both radio and chemo therapy.

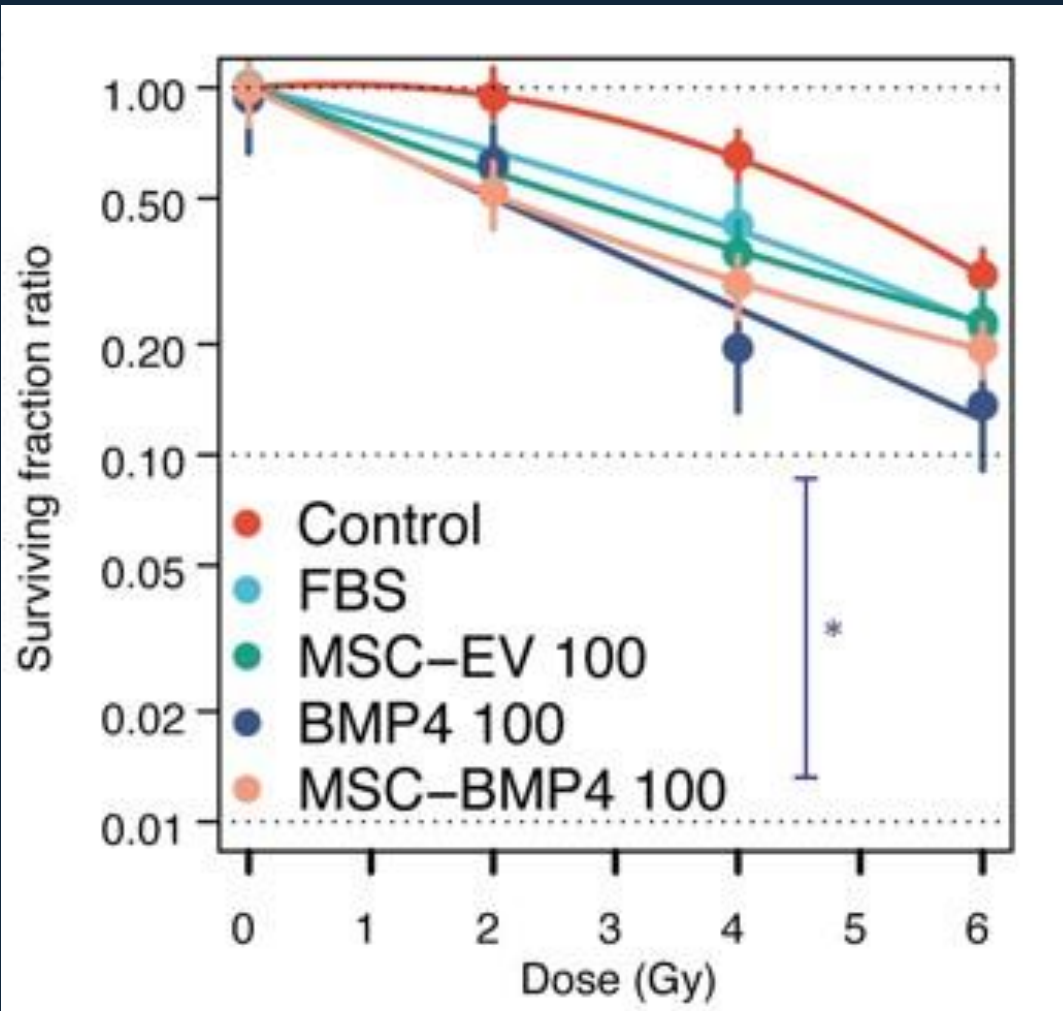


# Cancer stem cells / glioma stem cells (GSCs)



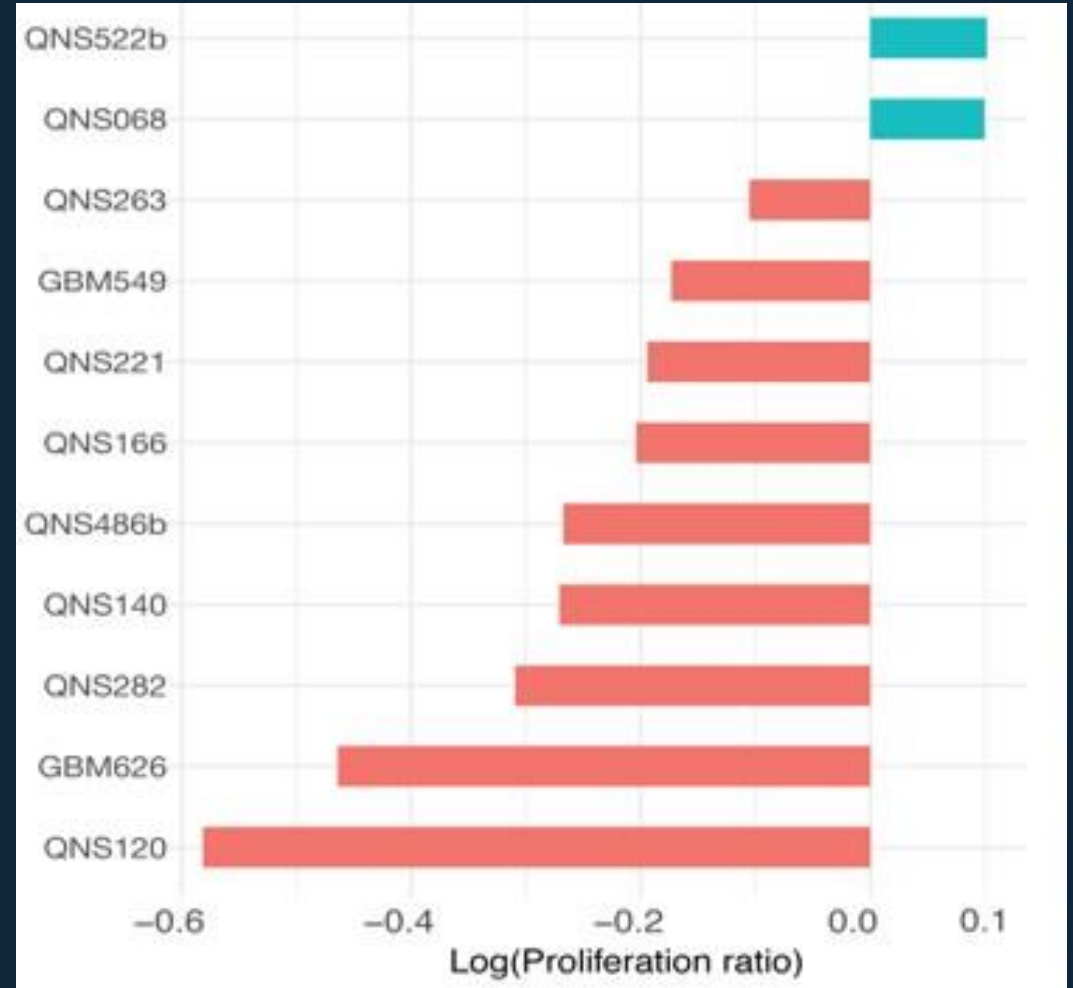
# BMP4 targets GSCs

BMP4 increases radiosensitivity of GSCs

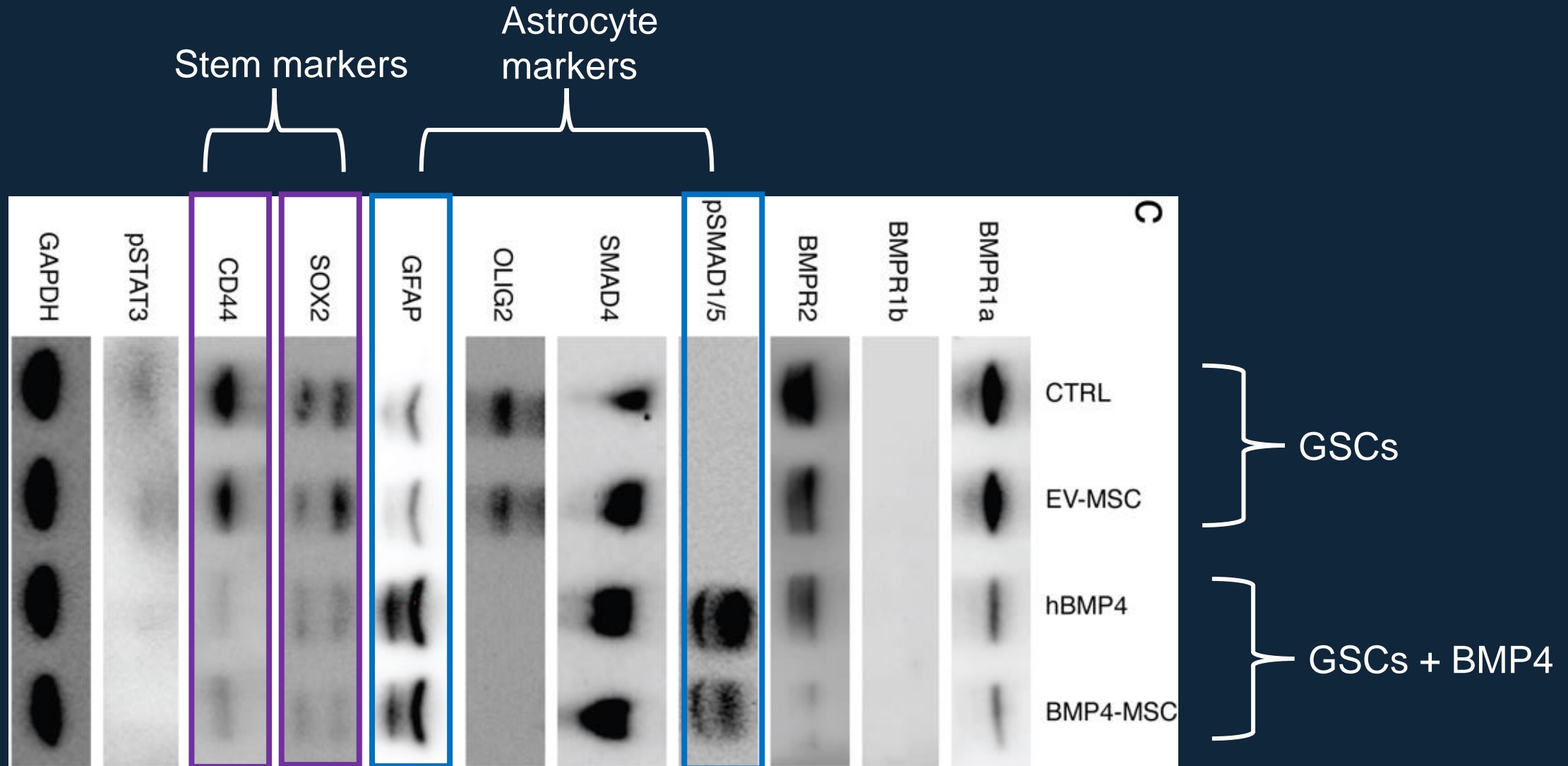


BMP4 decreases the proliferation rate of GSCs

Patient derived cell lines

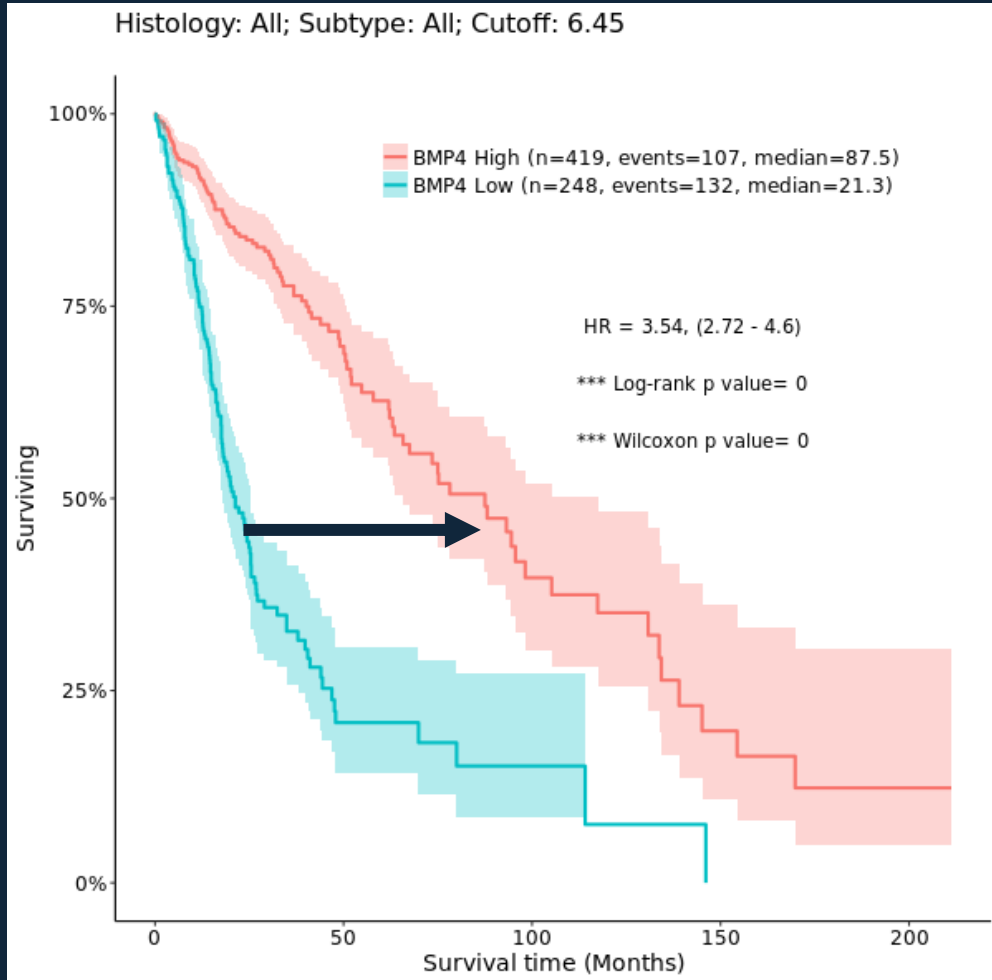


# BMP4 causes differentiation to astrocytic-like lineage

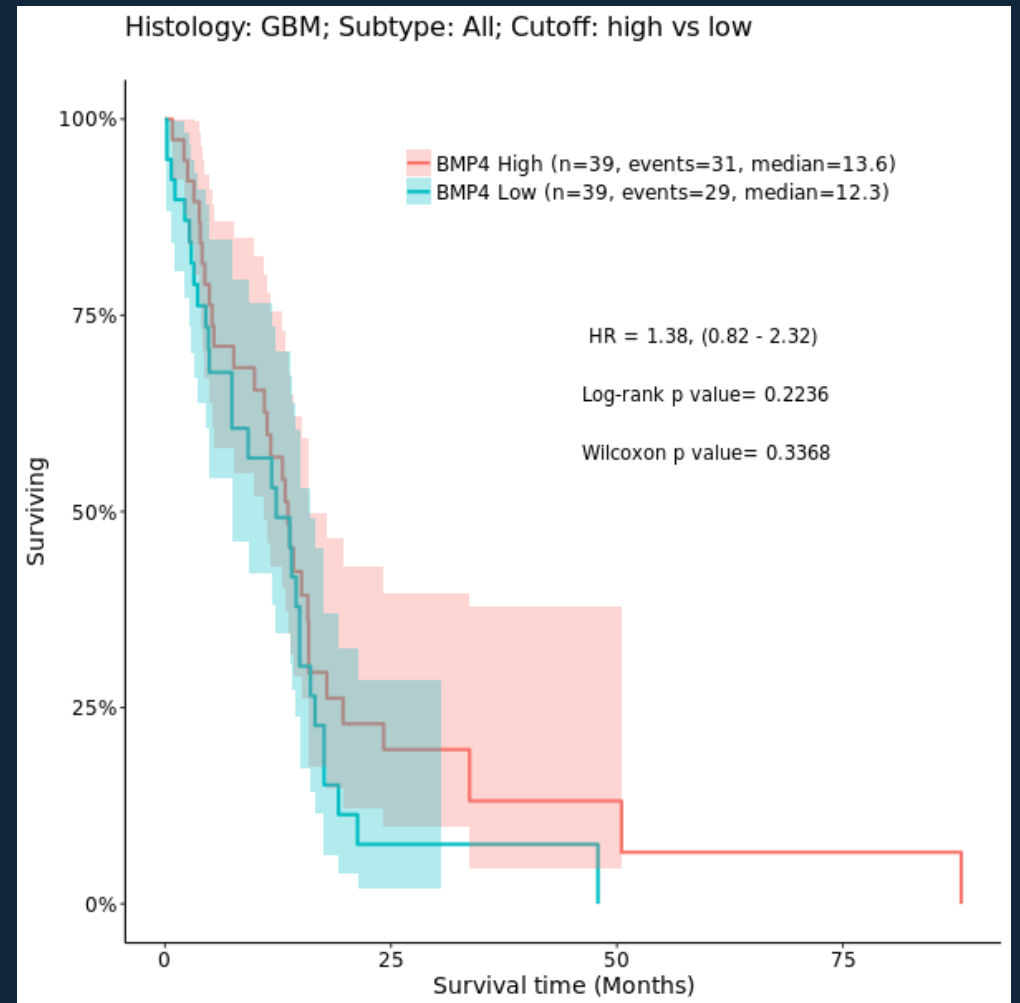


# BMP4 is prognostic in Glioma

Across all glioma subtypes

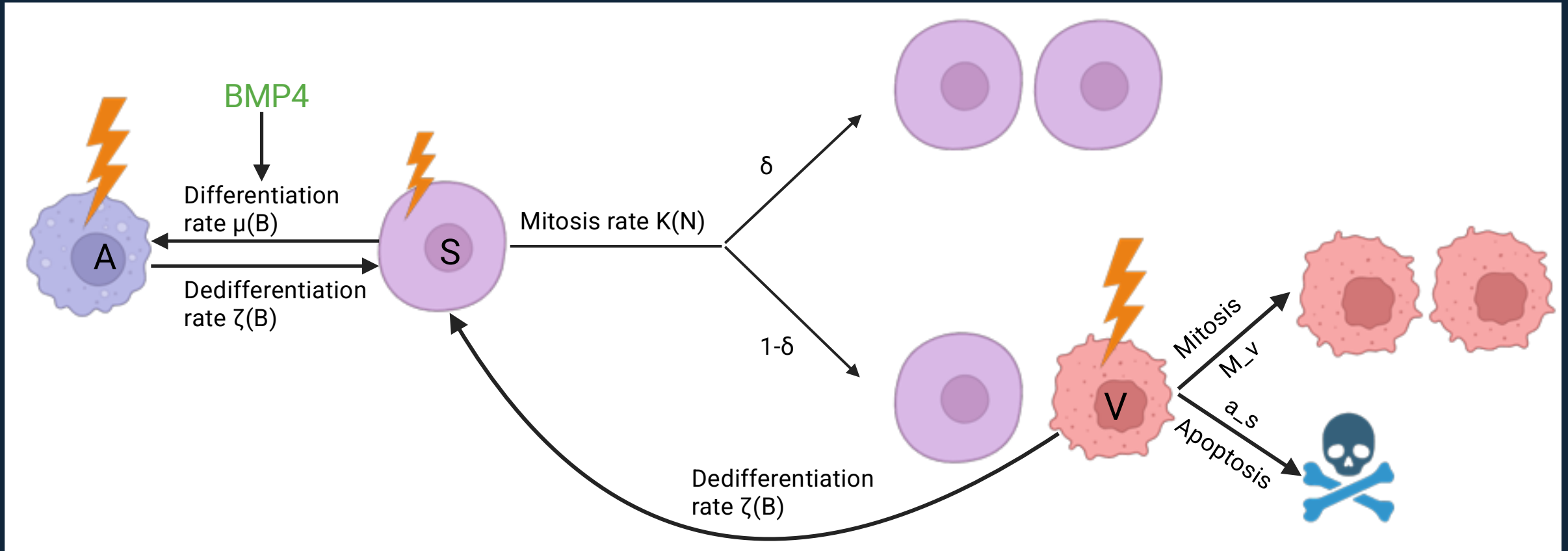


GBM only





# Stem cell model with BMP4

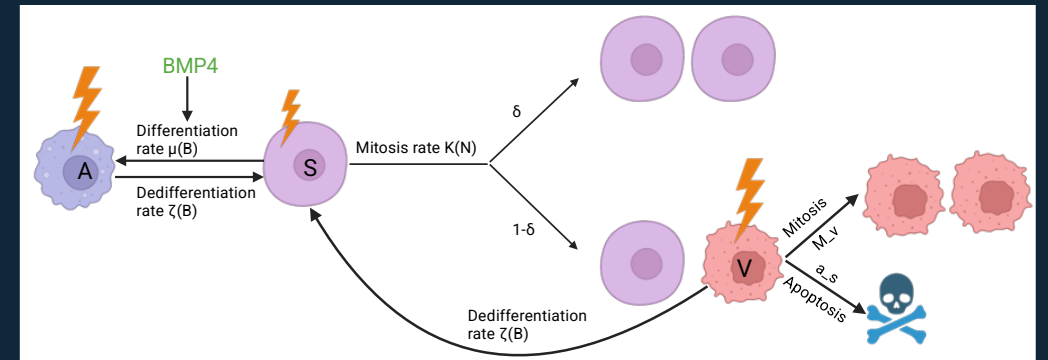


# Stem cell model with BMP4

$$\frac{ds}{dt} = \underbrace{\delta m_s K(N)s}_{\text{Symetric division of GSCs}} + \underbrace{\zeta(B)(a+v)}_{\text{Dedifferentiation of TCs and ALCs}} - \underbrace{\mu(B)s}_{\text{Differentiation}}$$

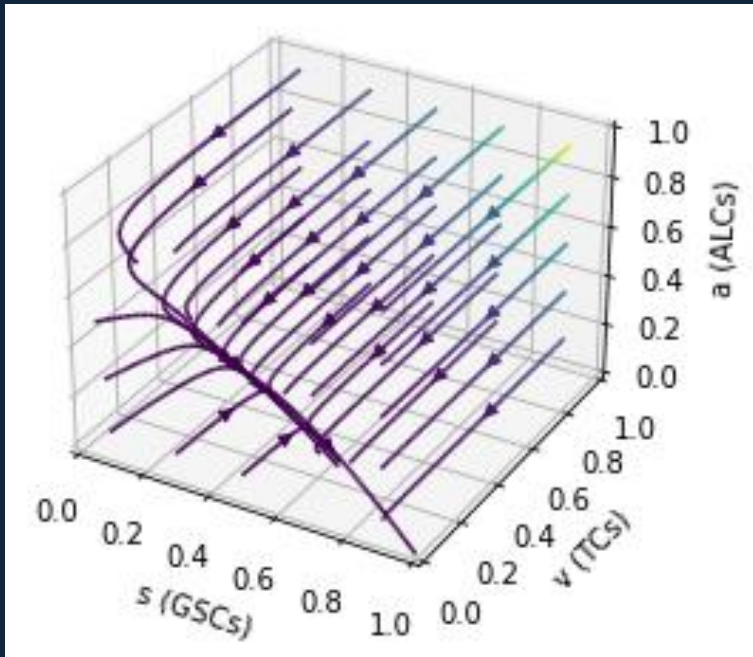
$$\frac{dv}{dt} = \underbrace{(1-\delta)m_s K(N)s}_{\text{Asymetric division of GSCs}} + \underbrace{m_v K(N)v}_{\text{Mitosis of TCs}} - \underbrace{a_v v}_{\text{Apoptosis of TCs}} - \underbrace{\zeta(B)v}_{\text{Dedifferentiation}}$$

$$\frac{da}{dt} = \underbrace{\mu(B)s}_{\text{Differentiation}} - \underbrace{\zeta(B)a}_{\text{Dedifferentiation}}$$



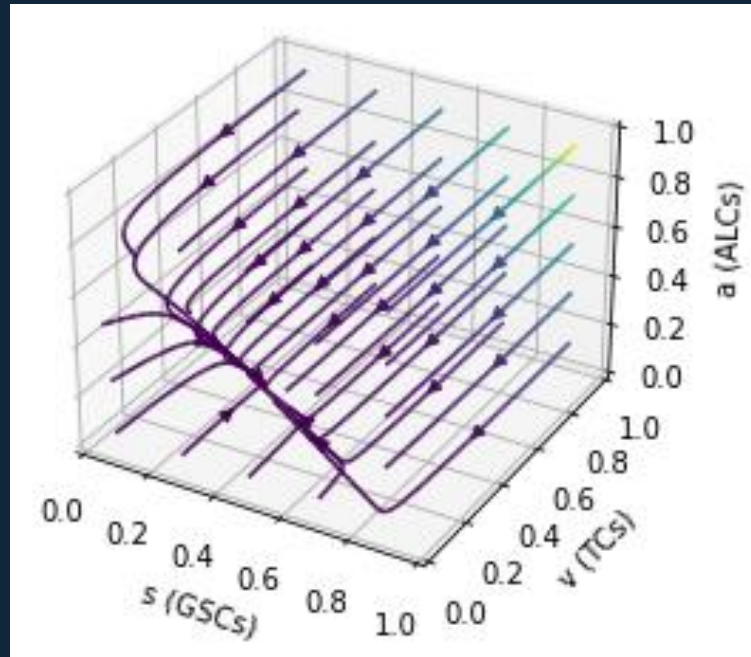
# Phase plane

No BMP4



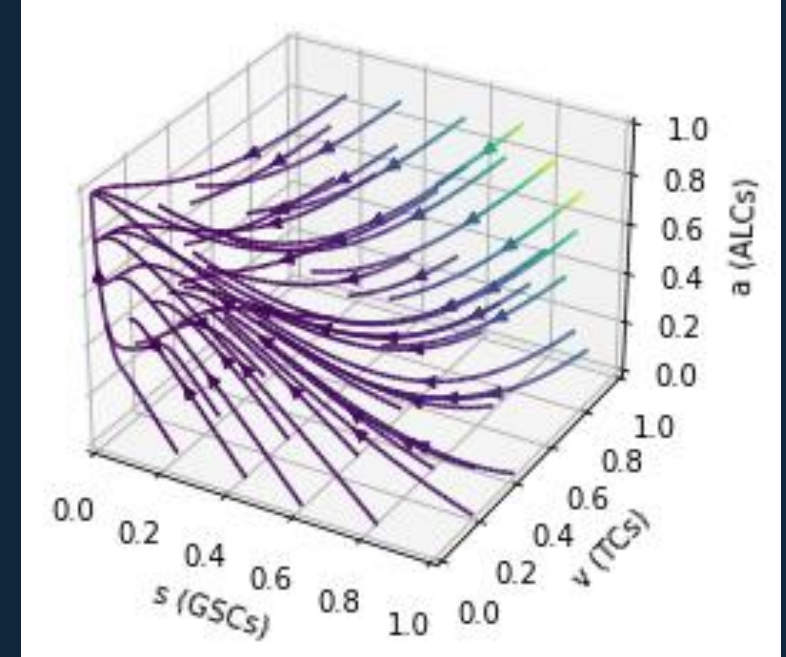
Steady state (1,0,0)

Low BMP4 (representing endogenous expression)



Steady state ( $s^*, 0, a^*$ )

High BMP4 (treatment)

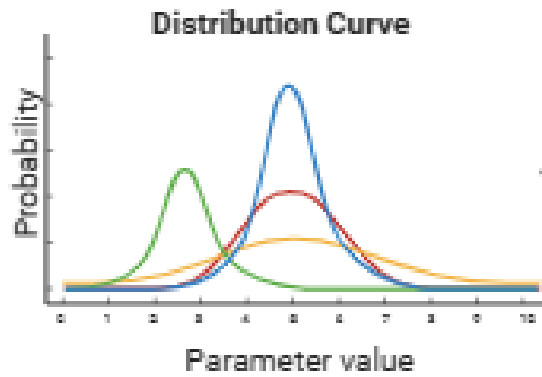


Steady state (0,0,1)

# Virtual clinical trial

## Virtual clinical trial pipeline

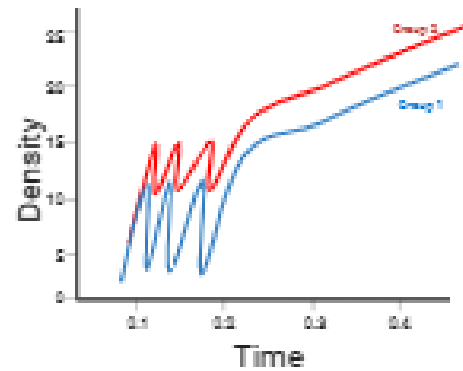
Determine patient specific parameters



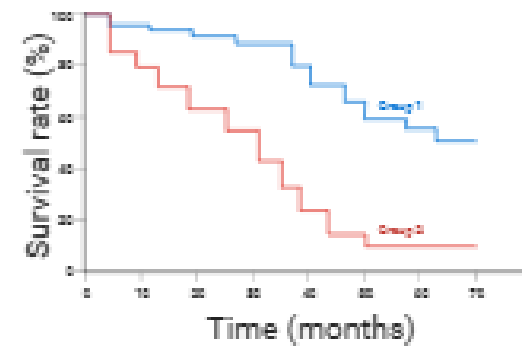
Generate a patient cohort / digital twins



Simulate treatment arms



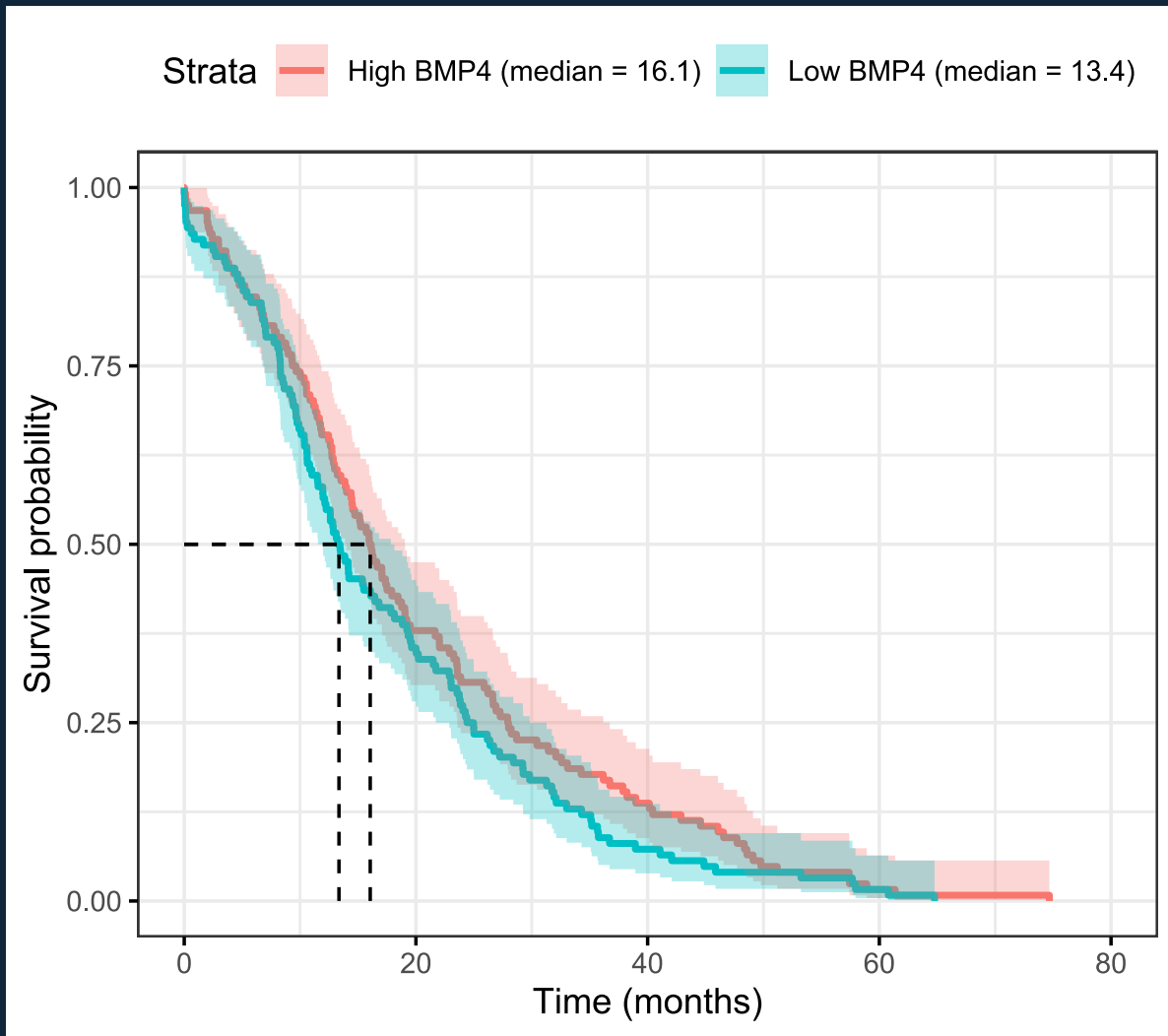
Calculate survival statistics



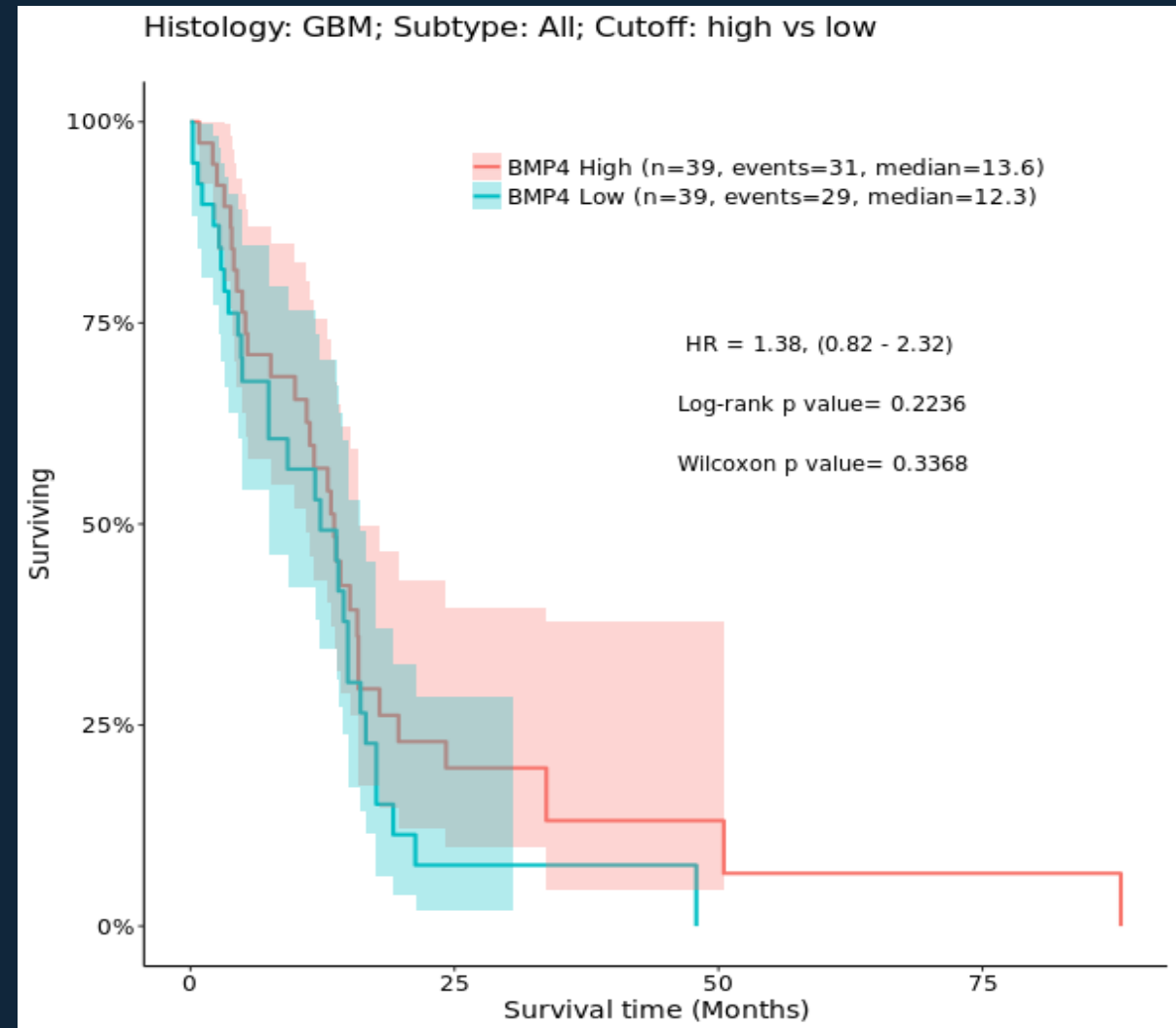
Patient specific parameters:  
 $m_s, m_v, \gamma_s, \gamma_v, \mu, ICs, B_{endo}$

# Virtual clinical trial

## Simulated data



## TCGA data



# Limitations and outstanding challenges

- More data for the parameter distributions is always better.
- BMP4 MSC delivery is still being developed (Mayo Florida hope to trial in canines).
- Large heterogeneity in response to BMP4 between patients.
- Biomarker for BMP4 responsiveness still being investigated (BMPR1a, PRb have shown promise)

# Mathematical Neuro-oncology lab



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